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By
(Signature of person mailing)
ROY F. WALDRON
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: J. W. Coe et al. :
Examiner: Not Yet Assigned
SER. NO.: Not Yet Assigned :
Group Art Unit: Not Assigned
FILING DATE: Concurrently Herewith :
TITLE: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS :

Commissioner for Patents
Box Patent Application
Washington, D.C. 20231

Sir:

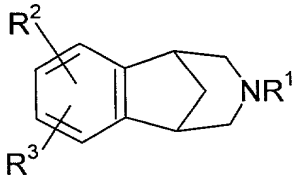
PRELIMINARY AMENDMENT

Prior to examination on the merits and calculation of filing fees, please enter the following amendments to the abstract, specification and claims. Marked up versions of the amendments to the abstract, specification and claims are found in the Appendix attached hereto.

IN THE ABSTRACT

at page 80, lines 7-12, delete the paragraph and insert the following new paragraph:

Pharmaceutical compositions comprising compounds of the formula



(I)

and their pharmaceutically acceptable salts, wherein R^1, R^2, and R^3 are defined as in the specification, in combination with another therapeutic agent and methods of using such combinations in the treatment of neurological and psychological disorders.

IN THE SPECIFICATION

at page 1, line 7, insert the following new paragraph:

This application is continuation application of U.S. Ser. No. 09/402,010, filed September 28, 1999, which is the National stage entry under 35 U.S.C. § 371 of PCT/IB98/01813, filed November 13, 1998 which claims the benefit of U.S. Provisional Application Ser. No. 60/070,245, filed December 31, 1997.

at page 1, lines 7-22, delete the existing paragraph and insert the following new one:

This invention relates to aryl fused azapolycyclic compounds, as defined more specifically by formula I below. Compounds of formula I bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Such compounds are useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome.

at page 3, lines 20-24, delete the existing paragraph and insert the following new one:

each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, -N-(C_1-C_6)alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

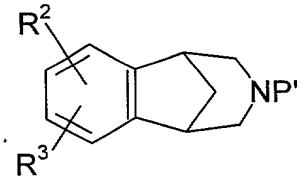
at page 5, after line 11, the following two new paragraphs are inserted:

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3 do not, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system.

Other embodiments of this invention relate to compounds of the formula I wherein one or both of R^2 and R^3 are $-C(=O)R^{13}$, wherein R^{13} is $(C_1\text{-}C_6)$alkyl. Further embodiments of this invention relate to compounds of the formula I wherein one or both of R^2 and R^3 are $-C(=O)R^{13}$, wherein R^{13} is $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_3)$alkyl optionally substituted with from one to seven fluorine atoms. Other embodiments relate to compounds of the formula I wherein one of R^2 and R^3 is CF_3, fluoro, cyano or C_2F_5.

at page 7, after line 14, insert the following new paragraph:

The invention also relates to a compound of the formula



(I′)

wherein R^2 and R^3 are defined above; and P′ is $COOR^{16}$ wherein R^{16} is allyl, 2,2,2-trichloroethyl or $(C_1\text{-}C_6)$alkyl; $-C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in claim 2; $-C(=O)H$, $-C(=O)(C_1\text{-}C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl, or t-butoxycarbonyl (t-Boc).

at page 8, line 22 to page 9, line 19, delete the existing two paragraphs and insert the following two new ones:

The present invention also relates to a method of treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age

related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

The present invention also relates to a pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias , gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

at page 9, line 26 to page 10, line 8, delete the existing paragraph and insert the following new one:

The present invention also relates to a method for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's

Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula

IN THE CLAIMS

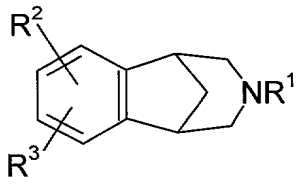
Cancel claims 7, 9 and 11-14.

Add new claims 15-35.

Replace claims 1-6, 8 and 10 with the clean copies of the amended claims are set forth below. Marked-up versions of the amended claims may be found in the Appendix attached hereto.

CLEAN COPY- ENTER

1. (Once Amended) A pharmaceutical composition comprising a compound of the formula



(I)

R^1 is hydrogen, (C_1 -C_6)alkyl, unconjugated (C_3-C_6)alkenyl, $XC(=O)R^{13}$, benzyl or -CH_2CH_2-O-(C_1-C_4)alkyl;

R^2 and R^3 are selected, independently, from hydrogen, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, nitro, amino, halo, cyano, -SO_q(C_1-C_6)alkyl wherein q is zero, one or two, (C_1.C_6)alkylamino-, [(C_1-C_6)alkyl]$_2$amino-, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$, -$XC(=O)R^{13}$, aryl-(C_0 -C_3)alkyl- or aryl-(C_0-C_3)alkyl-O-, wherein said aryl is selected from phenyl and naphthyl, heteroaryl-(C_0-C_3)alkyl- or heteroaryl-(C_0-C_3)alkyl-O-, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, and X^2(C_0-C_6)alkoxy-(C_0-C_6)alkyl-, wherein X^2 is absent or X^2 is (C_1-C_6)alkylamino- or [(C_1-C_6)alkyl]$_2$amino-, and wherein the (C_0-C_6)alkoxy-(C_0-C_6)alkyl- moiety of said X^2(C_0-C_6)alkoxy-(C_0-C_6)alkyl- contains at least one carbon atom, and wherein from one to three of the carbon atoms of said (C_0-C_6)alkoxy-(C_0-C_6)alkyl- moiety may optionally be replaced by an oxygen, nitrogen or sulfur atom, with the proviso that any two such heteroatoms must be separated by at least two carbon atoms, and wherein any of the alkyl moieties of said (C_0.C_6)alkoxy-(C_0-C_6)alkyl- may be optionally

substituted with from two to seven fluorine atoms, and wherein one of the carbon atoms of each of the alkyl moieties of said aryl-(C_0-C_3)alkyl- and said heteroaryl-(C_0-C_3)alkyl- may optionally be replaced by an oxygen, nitrogen or sulfur atom, and wherein each of the foregoing aryl and heteroaryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from (C_1-C_6)alkyl optionally substituted with from one to seven fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from two to seven fluorine atoms, halo, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, nitro, cyano, amino, (C_1-C_6)alkylamino-, [(C_1-C_6) alkyl]$_2$amino-, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

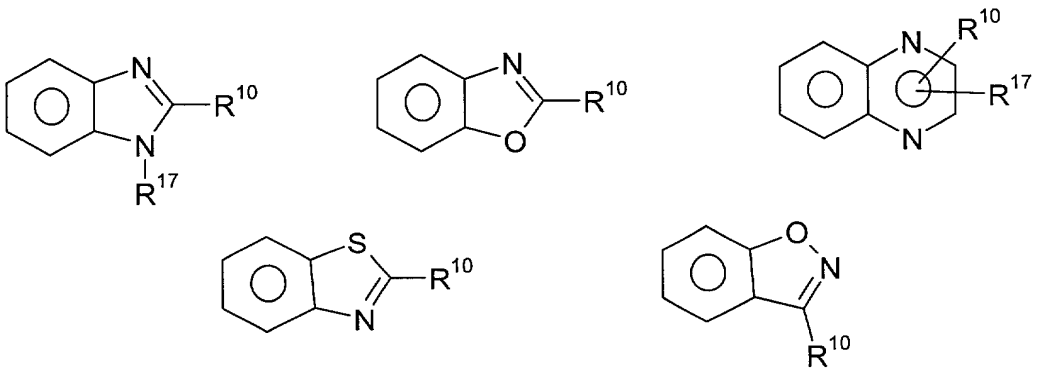
or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents, preferably from zero to two substituents for the monocyclic rings and from zero to three substituents for the bicyclic rings, that are selected, independently, from (C_1 -C_6) alkyl optionally substituted with from one to seven fluorine atoms, (C_1 -C_6) alkoxy optionally substituted with from one to seven fluorine atoms, nitro, cyano, halo, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1 -C_6)alkylamino and [(C_1 -C_6) alkyl]$_2$amino, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

wherein each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, -N-(C_1-C_6)alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, (C_1-C_6)alkylene;

and a compound that is selected from an antidepressant, a muscarinic agonist, a neurotrophic factors, an agent that slows or arrests Alzheimer's disease, an amyloid aggregation inhibitor, a secretase inhibitor, a tau kinase inhibitor, a neuronal antiinflammatory agent and estrogen-like therapeutic agent.

2. A pharmaceutical composition according to claim 1 wherein the compound of formula I is, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic ring system selected from the following:



wherein R^{10} and R^{17} are selected, independently, from $(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, cyano, halo, amino, $(C_1\text{-}C_6)$alkylamino-, $[(C_1\text{-}C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, phenyl and monocyclic heteroaryl, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur.

3. (Once Amended) A pharmaceutical composition according to claim 1 wherein the compound of formula I is, wherein R^2 and R^3 do not, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system.

4. (Once Amended) A pharmaceutical composition according to claim 1 wherein the compound of formula I is, wherein one or both of R^2 and R^3 are $-C(=O)R^{13}$ wherein R^{13} is $(C_1\text{-}C_6)$alkyl.

5. (Once Amended) A pharmaceutical composition according to claim 1 wherein the compound of formula I is, wherein one of R^2 and R^3 is $-COR^{13}$ wherein R^{13} is $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_3)$alkyl optionally substituted with from one to seven fluorine atoms.

6. (Once Amended) A pharmaceutical composition according to claim 1 wherein the compound of formula I is, wherein one of R^2 and R^3 is CF_3 , fluoro, cyano or C_2F_5.

8. (Once Amended) A method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount

of a pharmaceutical composition according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

10. (Once Amended) A method for treating a disorder or condition selected from inflammatory bowel disease, ulcerative colitis, pyoderma gangrenosum , Crohn's disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions; dependencies on, or addictions to, nicotine, tobacco products, alcohol, benzodiazepines, barbiturates, opioids or cocaine; headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, [including] petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment a pharmaceutical composition according to claim 1 that is effective in treating such disorder or condition.

15. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is selected from the group consisting of
2-fluoro-N-(4-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-5-yl)-benzamide;
1-(10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;
and pharmaceutically acceptable salts thereof.

16. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is selected from the group consisting of:
4-methyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-amino-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
N^1-[10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl]acetamide;
4,5-difluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-chloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
3-(10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-5-methyl-1,2,4-oxadiazole;
10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-ol;

4,5-dichloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

N^4,N^4-dimethyl-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonamide;

4-(1-pyrrolidinylsulfonyl)-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;

4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;

5-chloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;

4-ethynyl-5-chloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-fluoro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-chloro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;

4-ethynyl-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4,5-bistrifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

and pharmaceutically acceptable salts thereof.

17. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is selected from the group consisting of:

3-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

3-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl cyanide;

4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

and pharmaceutically acceptable salts thereof.

18. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is:

4-nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene; or a pharmaceutically acceptable salt thereof.

19. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is:

4,5-dichloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene; or a pharmaceutically acceptable salt thereof.

20. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is:

3-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene; or a pharmaceutically acceptable salt thereof.

21. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is:

3-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene; or a pharmaceutically acceptable salt thereof.

22. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is:

4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene; or a pharmaceutically acceptable salt thereof.

23. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is:

4-fluoro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene; or a pharmaceutically acceptable salt thereof.

24. (New) A pharmaceutical composition wherein the antidepressant is a tricyclic antidepressant or a serotonin reuptake inhibiting antidepressant.

25. (New) A pharmaceutical composition wherein the neurotrophic factor is NGF

26. (New) A pharmaceutical composition wherein the agent that slows or arrests Alzheimer's disease is a cognition enhancer.

27. (New) A pharmaceutical composition according to claim 1 selected from the group consisting of:

5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-neopentyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-7-neopentyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
and pharmaceutically acceptable salts thereof.

28. (New) A pharmaceutical composition according to claim 1 which is:
6-methyl-5-thia-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
or a pharmaceutically acceptable salt thereof.

29. (New) A pharmaceutical composition according to claim 1 which is:
6-methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
or a pharmaceutically acceptable salt thereof.

30. (New) A pharmaceutical composition according to claim 1 which is:
6,7-dimethyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
or a pharmaceutically acceptable salt thereof.

31. (New) A pharmaceutical composition according to claim 1 which is:
6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
or a pharmaceutically acceptable salt thereof.

32. (New) A pharmaceutical composition according to claim 1 which is:
5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
or a pharmaceutically acceptable salt thereof.

33. (New) A pharmaceutical composition according to claim 1 which is:
14-methyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
or a pharmaceutically acceptable salt thereof.

34. (New) A pharmaceutical composition according to claim 1 which is:
5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
or a pharmaceutically acceptable salt thereof.

35. (New) A pharmaceutical composition according to claim 1 which is:
7-methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene;
or a pharmaceutically acceptable salt thereof.

REMARKS

Applicants have amended the Abstract to correct the description of the variables as presented in the structure. Applicants have inserted a statement on page 1 of the application to indicate the priority required by 37 C.F.R. § 1.78. Applicants have corrected a number of typographical and spelling errors on pages 1, 3, 7, 8 and 9, as specifically set forth above.

Applicants have inserted text on page 5 relating to other embodiments of the invention that are fully supported by claims 3-6 as originally filed. The insertion of the text at page 7 of the structure of formula (I') and accompanying description has full literal support in claim 14 in the application as originally filed. The insertion of "obsessive-compulsive disorder" at pages 8 and 9 and claim 10 into the lists of diseases, disorders or conditions for which pharmaceutical compositions comprising the compounds of the invention, and methods employing those compounds/compositions is supported by the description at page 1, line 18.

Applicants have amended claim 1 to claim a pharmaceutical composition containing a compound of formula I in combination with a therapeutic agent. This amendment has support in the specification at page 1, lines 23-34. Further, Applicants have canceled claims 7, 9, and 11-14. Applicants have made these amendments and cancellations of claims without prejudice to file divisional application(s) drawn to the canceled subject matter. Applicants have amended claim 10 to correct several typographical, spelling and format errors.

New claims 15-23 through 27-35 set forth species corresponding to the invention and are supported by the Examples and the listed species in the specification at page 5-7. New claims 24-26 relate to specific therapeutic agents comprising the combination pharmaceutical composition of the invention.

All of the foregoing amendments have support in the application as filed. These amendments add no new matter to the application.

Applicants believe the present preliminary amendment renders the set of pending claims in condition for allowance and request the issuance of a Notice of Allowance. If a telephone interview would assist the furtherance of the prosecution of this application, the Examiner is invited to contact the undersigned.

Respectfully submitted,

Date: 2/14/2002

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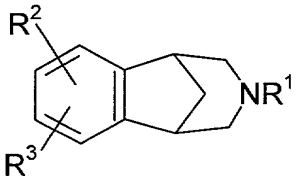
APPENDIX TO PRELIMINARY AMENDMENT

MARKED-UP VERSIONS OF AMENDED SPECIFICATION AND CLAIMS

IN THE ABSTRACT

at page 80, lines 7-12, delete the paragraph and insert the following new paragraph:

Pharmaceutical compositions [Compounds] comprising compounds of the formula



(I)

and their pharmaceutically acceptable salts, wherein R^1, R^2, and R^3 [and n] are defined as in the specification, [intermediates in the synthesis of such compounds, pharmaceutical compositions containing such compounds] in combination with another therapeutic agent and methods of using such [compounds] combinations in the treatment of neurological and psychological disorders [~~are claimed~~].

IN THE SPECIFICATION

at page 1, line 7, insert the following new paragraph:

This application is continuation application of U.S. Ser. No. 09/402,010, filed September 28, 1999, which is the National stage entry under 35 U.S.C. § 371 of PCT/IB98/01813, filed November 13, 1998 which claims the benefit of U.S. Provisional Application Ser. No. 60/070,245, filed December 31, 1997.

at page 1, lines 7-22, delete the existing paragraph and insert the following new one:

This invention relates to aryl fused azapolycyclic compounds, as defined more specifically by formula I below. Compounds of formula I bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Such compounds are useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, [amylotropic] amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac [arrythmias] arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive [supramuscular] supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, [barbituates] barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome.

at page 3, lines 20-24, delete the existing paragraph and insert the following new one:

each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, [piperizine, -N-(C_1-C_6)alkylpiperizine] piperazine, -N-(C_1-C_6)alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

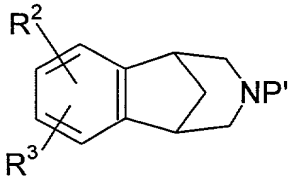
at page 5, after line 11, the following two new paragraphs are inserted:

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3 do not, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system.

Other embodiments of this invention relate to compounds of the formula I wherein one or both of R^2 and R^3 are -C(=O)R^{13}, wherein R^{13} is (C_1-C_6)alkyl. Further embodiments of this invention relate to compounds of the formula I wherein one or both of R^2 and R^3 are -C(=O)R^{13}, wherein R^{13} is (C_1-C_6)alkyl or (C_1-C_3)alkyl optionally substituted with from one to seven fluorine atoms. Other embodiments relate to compounds of the formula I wherein one of R^2 and R^3 is CF_3, fluoro, cyano or C_2F_5.

at page 7, after line 14, insert the following new paragraph:

The invention also relates to a compound of the formula



(I′)

wherein R^2 and R^3 are defined above; and P′ is $COOR^{16}$ wherein R^{16} is allyl, 2,2,2-trichloroethyl or (C_1-C_6)alkyl; -C(=O)NR^5R^6 wherein R^5 and R^6 are defined as in claim 2; -C(=O)H, -C(=O)(C_1-C_6)alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl, or t-butoxycarbonyl (t-Boc). --

at page 8, line 22 to page 9, line 19, delete the existing two paragraphs and insert the following two new ones:

The present invention also relates to a method of treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, [amylotropic] amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac [arrythmias] arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive [supramuscular] supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, [barbituates] barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a

mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

The present invention also relates to a pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, [amylotropic] amytrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac [arrhythmias] arrhythmias , gastric acid hypersecretion, ulcers, pheochromocytoma, progressive [supramuscular] supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, [barbituates] barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising an amount of a compound of the formula I, or a pharmaceutically [accepable] acceptable salt thereof, and a pharmaceutically acceptable carrier.

at page 9, line 26 to page 10, line 8, delete the existing paragraph and insert the following new one:

The present invention also relates to a method for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, [amylotropic] amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac [arrhythmias] arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive [supramuscular] supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, [barbituates] barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula

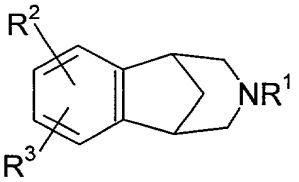
IN THE CLAIMS

Amend claim 1-6, 8 and 10.

Cancel claims 7, 9 and 11-14.

Add new claims 15-26.

1. (Once Amended) A pharmaceutical composition comprising a compound of the formula



(I)

R^1 is hydrogen, (C_1 -C_6)alkyl, unconjugated (C_3-C_6)alkenyl, $XC(=O)R^{13}$, benzyl or -CH_2CH_2-O-(C_1-C_4)alkyl;

R^2 and R^3 are selected, independently, from hydrogen, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, nitro, amino, halo, cyano, -SO_q(C_1-C_6)alkyl wherein q is zero, one or two, (C_1-C_6)alkylamino-, [(C_1-C_6)alkyl]$_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, aryl-(C_0 -C_3)alkyl- or aryl-(C_0-C_3)alkyl-O-, wherein said aryl is selected from phenyl and naphthyl, heteroaryl-(C_0-C_3)alkyl- or heteroaryl-(C_0-C_3)alkyl-O-, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, and X^2(C_0-C_6)alkoxy-(C_0-C_6)alkyl-, wherein X^2 is absent or X^2 is (C_1-C_6)alkylamino- or [(C_1-C_6)alkyl]$_2$amino-, and wherein the (C_0-C_6)alkoxy-(C_0-C_6)alkyl- moiety of said X^2(C_0-C_6)alkoxy-(C_0-C_6)alkyl- contains at least one carbon atom, and wherein from one to three of the carbon atoms of said (C_0-C_6)alkoxy-(C_0-C_6)alkyl- moiety may optionally be replaced by an oxygen, nitrogen or sulfur atom, with the proviso that any two such heteroatoms must be separated by at least two carbon atoms, and wherein any of the alkyl moieties of said (C_0-C_6)alkoxy-(C_0-C_6)alkyl- may be optionally substituted with from two to seven fluorine atoms, and wherein one of the carbon atoms of each of the alkyl moieties of said aryl-(C_0-C_3)alkyl- and said heteroaryl-(C_0-C_3)alkyl- may optionally be replaced by an oxygen, nitrogen or sulfur atom, and wherein each of the foregoing aryl and heteroaryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from (C_1-C_6)alkyl optionally substituted with from one to seven fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from two to seven fluorine atoms, halo [~~(e.g., chloro, fluoro, bromo or iodo)~~], (C_2-C_6)alkenyl, (C_2-C_6)alkynyl,

hydroxy, nitro, cyano, amino, $(C_1$-$C_6)$alkylamino-, $[(C_1$-$C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$ and $-XC(=O)R^{13}$;

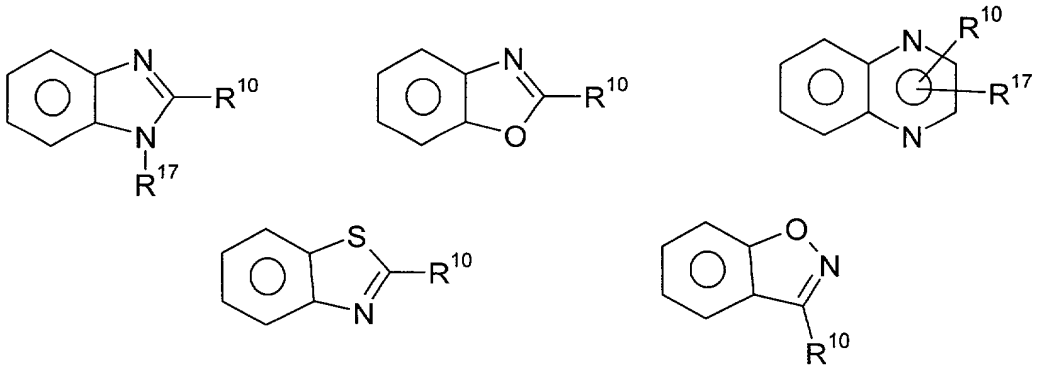
or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents, preferably from zero to two substituents for the monocyclic rings and from zero to three substituents for the bicyclic rings, that are selected, independently, from $(C_1$ -$C_6)$ alkyl optionally substituted with from one to seven fluorine atoms, $(C_1$ -$C_6)$ alkoxy optionally substituted with from one to seven fluorine atoms, nitro, cyano, halo, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy, amino, $(C_1$ -$C_6)$alkylamino and $[(C_1$ -$C_6)$ alkyl$]_2$amino, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$ and $-XC(=O)R^{13}$;

wherein each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and $(C_1$ -$C_6)$ alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, -N-$(C_1$-$C_6)$alkylpiperazine [~~piperizine, N-$(C_1$-$C_6)$alkylpiperizine~~] or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, $(C_1$-$C_6)$alkylene [~~;~~

~~with the proviso that: (a) at least one of R^1, R^2 and R^3 must be the other than hydrogen, and (b) when R^2 and R^3 are both hydrogen, R^1 cannot be hydrogen or methyl;~~] and a compound that is selected from an antidepressant, a muscarinic agonist, a neurotrophic factors, an agent that slows or arrests Alzheimer's disease, an amyloid aggregation inhibitor, a secretase inhibitor, a tau kinase inhibitor, a neuronal antiinflammatory agent and estrogen-like therapeutic agent.

2. A pharmaceutical composition according to claim 1 wherein the compound [~~according to claim 1~~] of formula I is, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic ring system selected from the following:



wherein R^{10} and R^{17} are selected, independently, from $(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, cyano, halo, amino, $(C_1\text{-}C_6)$alkylamino-, $[(C_1\text{-}C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, phenyl and monocyclic heteroaryl, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur [,] .

3. (Once Amended) A pharmaceutical composition according to claim 1 wherein the compound [~~according to claim 1~~] of formula I is, wherein R^2 and R^3 do not, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system.

4. (Once Amended) A pharmaceutical composition according to claim 1 wherein the compound [~~according to claim 1~~] of formula I is, wherein one or both of R^2 and R^3 are $-C(=O)R^{13}$ wherein R^{13} is $(C_1\text{-}C_6)$alkyl.

5. (Once Amended) A pharmaceutical composition according to claim 1 wherein the compound [~~according to claim 1~~] of formula I is, wherein one of R^2 and R^3 is $-COR^{13}$ wherein R^{13} is $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_3)$alkyl optionally substituted with from one to seven fluorine atoms.

6. (Once Amended) A pharmaceutical composition according to claim 1 wherein the compound [~~according to claim 1~~] of formula I is, wherein one of R^2 and R^3 is CF_3 , fluoro, cyano or C_2F_5.

8. (Once Amended) A method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a pharmaceutical composition [~~compound~~] according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

10. (Once Amended) A method for treating a disorder or condition selected from inflammatory bowel disease , [~~(including but not limited to~~] ulcerative colitis, pyoderma gangrenosum , [~~and~~] Crohn's disease [~~(~~)], irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic [~~amylotropic~~] lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac [~~arrhythmias~~] arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear [~~supramuscular~~] palsy, chemical dependencies and addictions; dependencies on, or addictions to, nicotine, tobacco products, alcohol, benzodiazepines, barbiturates, opioids or cocaine; headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), [~~chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI),~~] psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, [including] petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment [~~an amount of a compound~~] a pharmaceutical composition according to claim 1 that is effective in treating such disorder or condition.

15. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is selected from the group consisting of

2-fluoro-N-(4-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-5-yl)-benzamide;

1-(10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;

and pharmaceutically acceptable salts thereof.

16. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is selected from the group consisting of:

4-methyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-amino-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

N^1-[10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl]acetamide;

4,5-difluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-chloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

3-(10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-5-methyl-1,2,4-oxadiazole;

10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-ol;

4,5-dichloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

N^4,N^4-dimethyl-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonamide;

4-(1-pyrrolidinylsulfonyl)-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;

4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;

5-chloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;

4-ethynyl-5-chloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-fluoro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-chloro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;

4-ethynyl-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4,5-bistrifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

and pharmaceutically acceptable salts thereof.

17. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is selected from the group consisting of:

3-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

3-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl cyanide;

4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

and pharmaceutically acceptable salts thereof.

18. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is:

4-nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene; or a pharmaceutically acceptable salt thereof.

19. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is:

4,5-dichloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene; or a pharmaceutically acceptable salt thereof.

20. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is:

3-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene; or a pharmaceutically acceptable salt thereof.

21. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is:

3-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene; or a pharmaceutically acceptable salt thereof.

22. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is:

4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene; or a pharmaceutically acceptable salt thereof.

23. (New) A pharmaceutical composition according to claim 1 wherein the compound of formula I is:

4-fluoro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene; or a pharmaceutically acceptable salt thereof.

24. (New) A pharmaceutical composition wherein the antidepressant is a tricyclic antidepressant or a serotonin reuptake inhibiting antidepressant.

25. (New) A pharmaceutical composition wherein the neurotrophic factor is NGF

26. (New) A pharmaceutical composition wherein the agent that slows or arrests Alzheimer's disease is a cognition enhancer.

27. (New) A pharmaceutical composition according to claim 1 selected from the group consisting of:

5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-neopentyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-7-neopentyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

and pharmaceutically acceptable salts thereof.

28. (New) A pharmaceutical composition according to claim 1 which is:
6-methyl-5-thia-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
or a pharmaceutically acceptable salt thereof.

29. (New) A pharmaceutical composition according to claim 1 which is:
6-methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
or a pharmaceutically acceptable salt thereof.

30. (New) A pharmaceutical composition according to claim 1 which is:
6,7-dimethyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
or a pharmaceutically acceptable salt thereof.

31. (New) A pharmaceutical composition according to claim 1 which is:
6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
or a pharmaceutically acceptable salt thereof.

32. (New) A pharmaceutical composition according to claim 1 which is:
5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
or a pharmaceutically acceptable salt thereof.

33. (New) A pharmaceutical composition according to claim 1 which is:
14-methyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
or a pharmaceutically acceptable salt thereof.

34. (New) A pharmaceutical composition according to claim 1 which is:
5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
or a pharmaceutically acceptable salt thereof.

35. (New) A pharmaceutical composition according to claim 1 which is:
7-methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene;
or a pharmaceutically acceptable salt thereof.